Effects of indoor air pollution on clinical outcomes in patients with interstitial lung disease: protocol of a multicentre prospective observational study

Hee-Young Yoon,¹ Sun-Young Kim,² Jin Woo Song³

ABSTRACT

Background  Idiopathic pulmonary fibrosis (IPF) is a chronic progressive fibrosing interstitial lung disease with a poor prognosis. While there is evidence suggesting that outdoor air pollution affects the clinical course of IPF, the impact of indoor air pollution on patients with IPF has not been extensively studied. Therefore, this prospective multicentre observational study aims to investigate the association between indoor air pollution and clinical outcomes in patients with IPF.

Methods and analysis  This study enrolled 140 patients with IPF from 12 medical institutes in the Seoul and Metropolitan areas of the Republic of Korea. Over the course of 1 year, participants visited the institutes every 3 months, during which their clinical data and blood samples were collected. Additionally, indoor exposure to particulate matter ≤2.5 µm (PM2.5) was measured using MicroPEM (RTI International, Research Triangle Park, North Carolina, USA) in each participant’s house for 5 days every 3 months. Lung function was assessed using both site spirometry at each institution and portable spirometry at each participant’s house every 3 months. The study will analyse the impact of indoor PM2.5 on clinical outcomes, including mortality, acute exacerbation, changes in lung function, and health-related quality of life, in the participants. This study represents the first attempt to evaluate the influence of indoor air pollution on the prognosis of patients with IPF.

Ethics and dissemination  This study has received approval from the institutional review board of all participating institutions, including Asan Medical Center, Seoul, Republic of Korea (2021-0072).

Trial registration number  KCT0006217.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Several previous studies reported the association between air pollution and clinical outcomes in idiopathic pulmonary fibrosis (IPF), including mortality, acute exacerbation and disease progression. However, the most of these studies have focused on the effects of outdoor air pollutants, so there is a lack of comprehensive data on health effects of indoor air pollutants in patients with IPF.

WHAT THIS STUDY ADDS

⇒ Our study presents a comprehensive research protocol investigating the effects of exposure to indoor particulate matter ≤2.5 µm on patients with IPF. In addition, we are collecting a dataset that includes on-site and home lung function measurements, health-related quality of life and key clinical outcomes (such as death, acute exacerbation and hospitalisation) over a 1-year period, with regular blood sampling to assess biomarkers.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study can provide a basis for evidence-based policy-making, potentially reducing medical costs and improving the health of IPF patients by comprehensively assessing the impact of indoor air pollution on their health.

BACKGROUND AND RATIONALE

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic progressive fibrosing interstitial pneumonia with unknown aetiology. It has a poor prognosis, with a median survival of 3–5 years without treatment.¹⁻³ Several studies have demonstrated the harmful effects of air pollution on IPF prognosis, including incidence,⁴⁻⁵ acute exacerbation (AE),⁶⁻⁷ hospitalisation,⁸⁻⁹ changes in lung function,¹⁰⁻¹² and mortality.¹³⁻¹⁴

Particulate matter (PM) refers to the mixture of solid particles and liquid droplets found in the air. It is categorised into PM₁₀ (≤10 µm) or PM₂.⁵ (≤2.5 µm) based on their aerodynamic diameter.¹⁵ PM₂.⁵ is small enough to penetrate deeply into the lung parenchyma, leading to various harmful effects such as increased reactive oxygen stress, release of inflammatory cytokines and activation of inflammatory cells.¹⁶ In both in vitro and in vivo models, PM₂.⁵ exposure has been shown to promote the development of pulmonary fibrosis.¹⁷⁻¹⁹ Specifically, chronic exposure
of human bronchial epithelial cells to PM$_{2.5}$ results in the activation of the transforming growth factor-beta 1 (TGF-β1)/SMAD3 pathway, TGF-β1 excretion and epithelial–mesenchymal transition, which are known to promote the proliferation and activation of fibroblast. Additionally, exposure to PM$_{2.5}$ has been shown to increase the levels of profibrotic cytokines in the lungs, including TGF-β1 and connective tissue growth factor, in a bleomycin-induced pulmonary fibrosis model. Previous clinical studies have provided evidence that long-term exposure to PM$_{2.5}$ increases the mortality of IPF, whereas short-term exposure to PM$_{2.5}$ has been linked to the occurrence of AE or hospitalisation in patients with IPF. However, most previous investigations on the effects of air pollution have primarily focused on outdoor air pollution, overlooking the potential impact of indoor air pollution.

The concentration of indoor PM can differ significantly compared with that of outdoor PM due to various factors; these include the presence of indoor emission sources, infiltration rate of outdoor PM, ventilation system, use of air purifiers and seasonal factors such as window-opening tendencies during certain times of the year. Since patients with IPF are predominantly elderly individuals and have reduced exercise capacity, they tend to spend a significant amount of time indoors. Therefore, many IPF patients may be susceptible to the effects of indoor air pollution. Nevertheless, the impact of indoor air pollution on clinical outcomes in patients with IPF remains poorly understood. Therefore, the primary objective of our study is to examine the association between indoor PM$_{2.5}$ levels and clinical outcomes in patients with IPF who lives in Seoul and Metropolitan areas. We hypothesise that indoor PM$_{2.5}$ levels significantly affect the health outcomes in patients with IPF; here we describe the protocol of our study.

METHODS AND ANALYSIS

Aim and study design

This study is a prospective multicentre observational study to investigate the association between indoor PM$_{2.5}$ exposure and clinical outcomes in patients with IPF. Given the lack of previous studies on indoor PM$_{2.5}$ exposure in patients with IPF, the appropriate sample size required to achieve sufficient statistical power was uncertain. In order to ensure a robust analysis with a minimum of 100 participants, we enrolled 140 participants, considering the potential 30% drop-out rate observed in our preliminary study. This enrolment strategy guarantees the inclusion of over 100 participants in the final analysis. Patients with IPF were enrolled from 12 medical institutions located in Seoul and the Metropolitan areas of Republic of Korea, as shown in figure 1. After enrolment, the study participants were regularly followed up at 3-month intervals for a duration of 1 year. This study aimed to recruit patients from June 2021 to September 2022 and follow them for 1 year, with the final visit scheduled for October 2023.

Study population

The inclusion criteria for study participants were as follows: (1) patients diagnosed with IPF according to the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society/Latin American Thoracic Association statement in 2018; (2) those residing in the metropolitan area and (3) those with forced vital capacity (FVC) ranging 40%–80% predicted, or diffusing capacity for carbon monoxide (DLco) ranging 30%–80% predicted. Exclusion criteria were as follows: (1) current smokers, as their exposure to cigarette smoke could influence PM$_{2.5}$ measurements and confound the analysis and (2) patients aged <50 years, as the likelihood of IPF diagnosis in individuals below this age range is relatively low.
Clinical data collection

Baseline clinical data
At enrolment (visit 1), demographic data, including smoking status, comorbidities, medication history (use of antifibrotics, steroids or immunosuppressants), occupational history and address, were collected through medical records or patient interviews (table 1). The Charlson Comorbidity Index was calculated.23 Information on participant’s socioeconomic status (marital status, household income, education, employment) was collected through questionnaires and will be used as covariates in the health impact analysis. In addition, a survey was conducted during visit 1 to collect information on factors that may affect indoor air pollutant concentrations, including the distance from the residence to roads, traffic volume, cooking facilities, presence of mould, pets, year of construction and length of residency, chemicals used, ventilation methods, air purifiers, humidifiers, air conditioners, dehumidifiers and dryers.

Lung function
FVC and DLco were measured every 3 months at each institution according to the ATS/ERS recommendations.24-26 Additionally, FVC was measured using a portable spirometer (SPROLENIS, JNBIO, Chuncheon-si, Republic of Korea) every 3 months at each participant’s house, synchronised with the indoor air pollution measurement period. The measurement of FVC using portable spirometry was performed twice daily at 8:00 and 20:00 hours for 5 days to account for diurnal variability. All lung function results were expressed as percentages of the normal predicted values (% predicted).

Questionnaire for health-related quality of life
To assess the health-related quality of life (HRQL) of patients with IPF, two questionnaires were used: the King’s Brief Interstitial Lung Disease (K-BILD) and five-level EuroQol five-dimensional version (EQ-5D-5L). K-BILD is a brief, valid, specific questionnaire designed to measure the HRQL of patients with ILD.27 It consists of 15 items covering domains including breathlessness and activities, psychological and chest symptoms. K-BILD scores are weighted using logit transformation and range from 0 to 100. A Korean version of K-BILD, translated by a certified translator company (Mapi Language Services, Lyon, France), was used in this study. EQ-5D-5L is a health status measurement questionnaire developed by the EuroQol Group28 and is widely used for several conditions, including IPF.29 It consists of the EQ-5D descriptive section and the Visual Analogue Scale (VAS) section. The descriptive section assesses five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) on a five-point Likert scale. The results from the five dimensions are converted into a single index value between 0 and 1.30 VAS is a simple and easy-to-use tool that can provide visual information about a person’s subjective experience or phenomena, such as pain, quality of life and overall health. It consists of a vertical line with a fixed end point at each end, representing the minimum (0) and maximum (100) values. Higher VAS values indicate better health status. Korean versions of EQ-5D and EQ-VAS, translated using standardised protocols that comply with internationally recognised guidelines from the EuroQol Research Foundation (Rotterdam, Netherlands), were used in this study.

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Table 1 Study protocol for the assessment of health effect of air pollution on patients with interstitial lung disease

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K-BILD, The King’s Brief Interstitial Lung Disease; PM_{2.5}, particulate matter ≤2.5 μm; VAS, Visual Analogue Scale.
Clinical outcomes
The primary outcomes of this study were death, hospitalisation, AE, as well as changes in lung function and HRQL. AE of IPF was defined as acute worsening of dyspnoea typically within 30 days, accompanied by new bilateral lung infiltration that is not fully explained by heart failure or fluid overload and no identified extraparenchymal causes (pneumothorax, pleural effusion, pulmonary embolism). A decline of ≥10% in FVC is generally considered a surrogate marker for IPF mortality in clinical trials as it has been strongly related to mortality in IPF. In this study, disease progression was defined as a relative 10% decline in FVC predicted, calculated as

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\frac{100}{\text{FVC}_{\text{baseline}}} - \frac{\text{FVC}_{\text{baseline}}}{100}/\text{FVC}_{\text{baseline}}
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Sample collection
Blood samples (plasma, serum and DNA) were collected from participants using ethylenediaminetetraacetic acid (EDTA) tubes (BD Vacutainer EDTA Tubes, Becton, Dickinson and Company, New Jersey, USA) and serum separator tubes (SST) (BD Vacutainer SST Tubes, Becton, Dickinson and Company). Samples were stored frozen at −80°C until the measurement of biomarkers, including Krebs von den Lungen-6 (Nanopia KL-6 assay, SEKISUI MEDICAL, Tokyo, Japan), matrix metalloproteinase-7 (R&D Systems, Minneapolis, USA), surfactant protein-D (Biovender Laboratory Medicine, Karasek, Czech Republic) and chemokine ligand-18 (R&D Systems).

Measurement of indoor air pollution
The MicroPEM (RTI International, Research Triangle Park, North Carolina, USA) device is a lightweight PM exposure monitor that weighs only 240g and has three batteries. Figure 2A,B depicts the external and internal structures of MicroPEM, respectively. It has been widely used in previous clinical studies. MicroPEM combines real-time nephelometry and integrated referee filters for PM measurements. It includes an impactor and a light-scattering particle detector, with an airflow of 0.5 L/min. For real-time measurements, the MicroPEM samples PM$_{2.5}$ at a rate of 0.5L/min using light-scattering nephelometry every 10s. The concentration of PM$_{2.5}$ measured by the nephelometer is automatically corrected by embedded temperature and relative humidity sensors. Gravimetric and chemical analyses are conducted on the integrated filter to quantify the concentrations of PM$_{2.5}$ and its various chemical components. Gravimetric analysis can estimate the average PM$_{2.5}$ exposure concentration over a 24 hours period. Additionally, the filter is used to measure the mass of black carbon and brown carbon, as well as environmental tobacco smoke using a multi-wavelength optical absorption method. The 10s nephelometry PM$_{2.5}$ data are corrected and then integrated into a 1min average to be comparable to the average equals with the corresponding gravimetric concentration.

Participants visited each medical institution, and indoor air pollution at their homes was measured every 3 months for a 1-year period to assess seasonal variations in indoor air quality. Our measurement team visited each participant’s home and positioned the MicroPEM at the height of an adult’s waist in the space where participants spend most of their time, such as the living room or bedroom (figure 3A,B). During each season, indoor PM$_{2.5}$ measurements and home spirometry were performed on five consecutive days within a month of the patient’s clinic visit. In addition, we measured outdoor PM$_{2.5}$ in 20% of the homes of our study participants (n=24), who were randomly selected, living on the fifth floor or lower for safety reasons, to assess the infiltration of outdoor PM$_{2.5}$ into the indoor environment (figure 3C,D). We will estimate the infiltration using the ratio of indoor to outdoor concentrations of sulphur in PM$_{2.5}$, which has negligible indoor sources.

Statistical analysis
The PM$_{2.5}$ concentration will be analysed as a continuous variable and also categorised into quartiles due to the lack of specific indoor PM$_{2.5}$ concentration thresholds. The continuous variables will be expressed as mean±SD, while categorical variables will be expressed as number (percentages). Student’s t-test or Mann-Whitney U test will be used for continuous data, and the χ$^2$ test or Fisher’s
exact test for categorical data. Pearson’s or Spearman’s correlation analyses will be used to assess the correlation between PM concentrations and the health outcomes after testing of normality assumption. Paired t-test or Wilcoxon signed rank test will also be used to compare changes in clinical parameters between each visit. We will analyse repeated measurements using a linear mixed model, adjusting for covariates such as age, sex, smoking status, baseline FVC and DLco, while including a random intercept for each participant to account for intra-individual variability. Kaplan-Meier survival curves will be used to evaluate the occurrence of clinical outcomes. The Cox proportional hazards analysis will be used to identify risk factors of time-to-event clinical outcomes (death, AE, disease progression), and variables with a p<0.1 in the unadjusted analyses will be included in the multivariable analysis. For subgroup analysis, we will consider the severity of IPF according to the Gender-Age-Physiology index. In addition, we will perform a further analysis in which patients will be divided into two different groups: those affiliated to specialised tertiary hospitals for ILD and those from other healthcare institutions. A p<0.05 will be considered significant (two tailed). All statistical analyses will be performed using Statistical Package for the Social Sciences V.23.0 (IBM).

Regulatory aspects

Participant safety

Any potential risks to the study participants were carefully managed by ensuring that all aspects of recruitment and data collection were overseen by fully trained, experienced and competent research staff. The recruitment team included pulmonologists and research nurses with a strong background in both research methodology and clinical practice. The data collected were securely stored and individual details will be documented in a centrally monitored electronic case report form (https://icreat2.nih.go.kr/) under the supervision of the Korea National Institute of Health. Personally identifiable information was encrypted, and access was strictly limited to authorised individuals with research approval, ensuring the confidentiality and security of personal information.

Unexpected findings during examinations

During the informed consent process, participants were informed that the research team has a duty of care to inform or raise the issue if required by law, or if there are health concerns that require urgent attention during routine appointments.

Dissemination

The findings from the data analysis will be disseminated in a variety of ways, including abstracts, posters and presentations at conferences, and the publication of research manuscripts in peer-reviewed journals. In addition, these findings will be communicated to government agencies at the local levels, thereby contributing to policy formulation. Detailed reports will also be provided to the funding agencies, institutes and hospitals that supported and participated in the cohort study. Members of the study team will be granted the right to publish and claim authorship in accordance with the principles outlined in the ethical guidelines and authorship criteria.

Contributors JWS took full responsibility for the content of this manuscript. JWS made substantial contributions to the conception and design of the study. S-YK was responsible for establishing the indoor measurement process. H-YY and JWS drafted the initial manuscript. All authors discussed the results and reviewed the manuscript.

Funding This study was supported by grants from the Basic Science Research Programme (NRF-2022R1A2B5B00201602), the Bio & Medical Technology Development Programme (NRF-2022M3A9E4082647) of the National Research Foundation of Korea (NRF) funded by the Ministry of Science & ICT, Republic of Korea; the National Institute of Health research project (2021ER120701) and Korea Environmental Industry & Technology Institute through Core Technology Development Project for Environmental Diseases Prevention and Management Programme funded by Korea Ministry of Environment (RS-2022-KE002197), Republic of Korea.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patients.

Ethics approval This study involves human participants and the study was approved by the Institutional Review Board of Asan Medical Center (2021-0072). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The data supporting the findings of this study are available upon reasonable request from the corresponding author.

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